ISSN 1022-7954, Russian Journal of Genetics, 2015, Vol. 51, No. 10, pp. 939–948. © Pleiades Publishing, Inc., 2015.
Original Russian Text © V.A. Mglinets, 2015, published in Genetika, 2015, Vol. 51, No. 10, pp. 1097–1107.

REVIEWS AND THEORETICAL ARTICLES

Genetics of Lens Development

V. A. Mglinets
Medical Genetics Research Center, Moscow, 115478 Russia
e-mail: mglinetz@mail.ru
Received October 28, 2014

Abstract—The paper discusses the current data on the genetics of the lens development. Genetically based processes of the formation of the lens anlage, as well as its specification and differentiation, are considered. The main genes responsible for these consecutive processes of lens development are presented. Their mutational disorders can lead to the absence or underdevelopment of the lens or multiple types of cataracts.

Keywords: neural crest, lens, lens morphogenesis, eye development, placode, signalling, zebrafish.
DOI: 10.1134/S1022795415080050

INTRODUCTION

We previously provided an overview of works concerning the formation of the cornea from the presumptive eye ectoderm region [1]. Here, we will consider how the lens anlage differentiates and develops from the multipotent region of the head ectoderm, which produces the lens, cornea, and conjunctival epithelium, as well as the lacrimal glands and epidermis of the eyelids. This multistep process begins with the formation of future placode tissues from the ectoderm and their subsequent genetic specification [2] and ends with the formation of an avascular, transparent, and highly refractive lens structure capable of focusing light images onto the retina due to its lenticular shape.

FORMATION OF AN INTERMEDIATE STRIP OF TISSUE

During embryonic gastrulation, the ectoderm is divided into neural and nonneural ectoderm, forming an intermediate region between them. In the emerging neural domain (neural plate), neural genetic markers are expressed, such as *ERN1* (early response to neural induction), *Sox3* (related to Y-centered sex determining gene *SRY*, with domain *HMG-box*), *SoxD*, and *Geminin* (neural fate determination). The nonneural ectoderm reveals the expression of other genes, such as *Gata2, Gata3* (with the motif of recognizing consensus GATA), *Dlx-3*, *-5* (homeobox gene causing lack of distal parts), *Foxi3* (gene with domain *Forkhead box I3*), *Bmp4* (bone morphogenetic protein), and *Msx1* (muscle segment homeobox gene) [2]. The marker genes of both of the types mentioned above are expressed in the early neurula stage in the border region between the neural plate and ectoderm. BMP signaling proteins are involved in the regulation of gene expression by means of epidermal activation and the suppression of neural cell characteristics, and they determine the location of the intermediate region between the two tissues and its expression of genes specific to the border strip (*Dlx*, *Foxi1*, and *Msx*) [3]. Factors of the FGF (fibroblast growth factors) family participate in providing the ectodermal cells with certain characteristics of the border region and its further partitioning into the neural crest and the placode chain. In this process, a certain role is also played by the transforming growth factor beta TGFβ, which participates in the activation of gene *Smad3* (from *SMA* (small body size) + *mad* (maternal effect against decapentaplegic)) and Wnt signaling (*Wg* (wingless gene of *Drosophila*) + *Int* (gene for the integration of oncogenic viruses in vertebrates)) [4], which will be discussed further.

The role of the Dlx gene family, *Dlx3* [5, 6], *Dlx5* [7], and *Dlx6* [8], is to counter the formation of the neural plate in the border region. These genes are involved in the isolation and specification of longitudinal strips of progenitor cells for the neural crest and placodes. The *Foxi1* gene is also one of the early participants in the formation of the border region between the neural plate and ectoderm.

FUTURE PLACODE TISSUE FORMATION

The formed border region divides into the future placode tissue and the neural crest tissue. It has been found that a combination of FGF factors with *Wnt* and *BMP* gene expression antagonists induces the intact ectoderm to produce ectopic preplacodal tissue [9], indicating the involvement of these genes in isolation of the future placode strip. The future placode strip (pan- or preplacodal region) in the form of a horseshoe surrounds the rostral part of the neural plate and goes in the caudal direction along the prospective forebrain, midbrain, and hindbrain. The expression of

genes *Dlx5* and *Dlx3* in this strip increases the expression of preplacodal gene *Six1* (a homeobox homolog of the *sine oculis* gene (no eyes) of *Drosophila*) [10, 11] and *Six4* [12, 13], which contain the Six-domain and homeodomain. The expression of a dominant negative form of *Six1* causes a decrease in the number of cells expressing *Pax6* (a homeobox gene with the *Paired box* domain) in the lens placode. However, the expression of these genes is still not enough to activate the genes involved in the development of the future placode tissue, including *Pax6*, which plays a huge role in this process. This is indicated by the fact that, in the absence of the *Dlx* function, the Msx proteins inhibit the formation of placodes. In addition to genes *Six* and *Msx*, there is expression of genes from the Eya family (no eyes): *Eya1* and *Eya2* [14, 15], which are controlled by the higher-level genes [16] (including gene *Fgf8*) [17] and genes of anti-BMP and anti-Wnt signals originating from the neural plate and endomesoderm [9, 18]. It is known that the transcription factor encoded by *Six3*, although weakly interacting with *Eya*, interacts with its corepressors of the Groucho family [19]. The *Six3* expression pattern is similar to that for *Pax6*. The action of Six3 in the presumptive lens ectoderm does not depend on *Pax6*; *Six3* expression and localization in the nucleus in the lens placode later become related to *Pax6* activity [20]. *Six3* itself is involved in maintaining the expression of *Pax6* [21].

In mice, a similar situation is observed with respect to *Sox2*. At the preplacodal stage, its expression does not depend on *Pax6*: its activity requires *Bmp7* activity in the head ectoderm cells, whereas its expression in the lens placode is maintained by the functioning of *Pax6*. The expression of *Sox2* in mice in the eye vesicle and head ectoderm broad domain, including the presumptive lens ectoderm, in addition to *Bmp7*, also requires the expression of *Bmp4*. It is assumed that factor BMP4, on the one hand, activates lower-level genes of the optic vesicle and, on the other hand, serves as one of many inductive signals originating therefrom, causing the expression of *Sox2* in the optic vesicle and subsequent formation of the lens.

Cells of the strip of all future placodes are first specified, apparently as those of the lens. All of them first express their characteristic genes: *Sox2* [22], *Pax6*, *L-maf* (musculo-aponeurotic fibrosarcoma oncogene), *Foxc1*, and the genes of δ-crystallin and αB-crystallin [23]. Part of the future placode strip surrounding the rostral area of the neural plate, in addition to the aforementioned genes, later begins to express genes specific to the anterior placodes: *Otx2* (a homeobox gene, homolog of *ocelliless* (no eyes) of *Drosophila*) [24], *Six3* [25, 26], *Pitx3* (a pituitary homeobox gene), *Dmbx1* (a diencephalon/mesencephalon homeobox gene), and the gene of αA-crystallin, whereas cells of the posterior part express *Irx* (the *iroquois* homeobox gene), *Irx1*, *Irx2, Irx3*, and *Gbx2* (the gastrulation brain homeobox gene) [25, 27–29]. Neighboring preplacodes can have common markers. For example, genes of the *POU* family (*Pit*/*Oct*/*Unc*), genes *Oct-1*/*Pou2fl* (octamer transcription factor/*POU* domain factor), *Sox2*, and *Pax6* are used for inducing both lenticular and nasal placodes. At the same time, Pax6 and Pou2f1 (*Oct1*) are partners in the production of *Sox2* [30, 31]. It was shown that N-cadherin (cadherin 2—Cdh2) is expressed in these placodes in a Sox2-dependent manner. The expression of *Pax6* [32], which spread originally in the preplacodal ectoderm, including both the presumptive lens and nasal ectoderm, and later in the cells of the nasal predecessors, becomes completely suppressed. It was also noted that *Six1* is expressed in the lenticular and otic placodes, as well as the trigeminal nerve placode, thus confirming that cells of various placode anlages require *Six1* gene activity or *Six1*-related activity [33]. It is yet unclear on the basis of what positional information the expression of genes is restricted.

LENS PLACODE FORMATION

In the process of further development, the respective presumptive ectoderm cells adjacent to the optic vesicle elongate and form a thickened portion of tissue, a lens placode. Now the activity of genes *Sox2* [34], *Sox3* [32, 34], *Meis1* (a homeobox gene with myeloid ectopic viral integration site), and *Meis2* [35] is restrained by the presumptive lens ectoderm cells contacting the optic vesicle cells. The Sox proteins now form a complex with the Pax6 protein, for example, on δ-crystallin enhancer [30], and the interaction leads to their mutual activation [30, 36], resulting in the induction of the δ-crystallin gene [30] and *L-Maf* [37, 38]. Proteins of the Maf family are partners for Sox proteins and have a determinant critical value for them. It was found that the δ-crystallin gene enhancer in chickens, in addition to the binding site of the Sox–Pax6 complex [39, 40], contains two Maf-binding sites. The mouse γ*F*-crystallin gene promoter also contains binding sites for proteins Maf and Sox [40].

The formation of the lens placode also involves genes *Otx2* [32], *Otx1* [41], and *Hes1*/*Hes4* (*hairy and enhancer of split*) [26], as a result of which the presumptive lens ectoderm acquires the specific features of the lens placode [31]. *Otx2* encodes a bicoid-type homeodomain protein that is a regulator of the enhancer for *FoxE3*, a gene for lens differentiation in the presumptive lens ectoderm of *Xenopus* embryos. It is also known that *Otx2* controls the activity of genes *Pax6*, *Six3*, and *Notch2* but does not affect the expression of *Dlx5* [26].

The expression of *Hes4* directly depends on the activity of *Rx* (a retinal and anterior neural fold homeobox gene) expressed in the adjacent presumptive area of the retina and the neural plate [42] and may initially depend in the preplacodal ectoderm on the activity of *Notch2* [43]. Activated via Notch, the suppressor protein Su(H)/RBP-Jκ in turn directly activates the *FoxE3* gene enhancer in the presumptive lens

ectoderm. In *Xenopus* and mice, the expression of the Pitx3 factor containing homeodomain first appears in the lens placode [44] after the activation of *FoxE3*. *Hes1* is found in the preplacodal ectoderm in mice before the closing of the neural tube, and its expression in the developing lens placode persists [45].

As was mentioned above, *Pax6* is important not only for isolating the presumptive lens ectoderm but also for the proper formation of the lens placode. In mice, conditional deletion of the *Pax6* allele in the preplacodal presumptive lens ectoderm leads to a lack of the lens placode [46]. In the presumptive lens ectoderm, the dominant negative form of *Pax6* [37] inhibits the expression of *L-maf*, *Prox1*, and the δ-crystallin gene but not *Sox2* or *Six3*, leading to the impossibility of the formation of the lens placode. On the other hand, the *Pax6*^{Sey1Neu} allele, which represents a point mutation resulting in a nonfunctional protein, preserves both the expression of *Pax6* in the surface ectoderm of the head and the formation of the placode but leads to a lack of further expression of *Pax6* in the lens placode. This indicates that the action of *Pax6* has two expression phases [47]: in the presumptive ectoderm and in the lens placode. These two phases are apparently controlled by different enhancers, *EE* and *SIMO*. *SIMO* was first discovered in patients with aniridia, in which it exists as a conserved region separated from the coding region of *Pax6* [48]. The *Pax6* enhancer *EE* was identified as a binding site of Meis factor; this indicates regulation of the enhancer by homeodomain transcription factors Meis1 and Meis2, which belong to the TALE class (three amino acid loop extension) with a characteristic loop of three amino acids [35]. The activity of *EE* is controlled by the Pax6 factor, as well as the proteins Sox2 [36], Pou2f1 [31], and Prep1 (PROP paired-like homeobox protein 1) [49]. The protein of *Prep1*, also belonging to the TALE family, modulates the time and expression levels of *Pax6* [49]. The expression of *Pax6* in the stage of the lens placode formation is also controlled by *Bmp7*. It is assumed [47] that Pax6 autoregulation can be controlled by MAPKs (mitogen-activated protein kinases). Let us note that the signal chain Fgf comprises the Ras–Raf–MAPK pathway as one of the branches. It has been shown in mice that the expression of *Pax6* actually requires FGFR (fibroblast growth factor receptor) signaling [50]. For example, in the case of a dominant-negative mutation in *FgfR1*, the formation of the lens placode reveals early defects and reduced expression of *Pax6*. The expression of *Pax6* in the formation of the lens placode in mice also requires the suppression of Wnt/β-catenin signaling [51]. It is noted that elimination of the β-catenin gene expression leads to the formation of ectopic lenses in the periocular ectoderm in [52], as well as the partial recovery of the formation of lenses in an *Rx*-deficient mouse embryo completely deprived of retinal tissue. This suggests a role of the presumptive retina in lens induction, which is most likely connected with the suppression of Wnt/β-catenin signaling in the presumptive lens ectoderm [4]. Let us only note that the induction of the lens is also apparently affected by the expression of *Pax6* in retinal progenitors [53].

OPTIC VESICLE FORMATION

In chick and mouse embryos, the thickened lens placode invaginates in the direction of the optic vesicle and detaches in the form of the optic vesicle from the head ectoderm [54]. Mice knockout for *Mab21l1* (*male abnormal 21*-like *1*) form a lens placode that is incapable of invaginating due to cell proliferation disorders [55]. This defect affects the expression of *FoxE3* and *Pdgfr*α (alpha-type platelet-derived growth factor receptor) and the expression of *Prox1* (*prospero* homeobox gene 1). It is shown that separation of the optic vesicle from the surface ectoderm requires Jag1 (jagged 1) and Rbpj (recombination signal binding protein for immunoglobulin kappa J region) proteins, which are involved in Notch signaling. It is known that *Pitx3* is also important for this process in mice [44]. The protein Sip1, which interacts with *Smad* and is coexpressed with epithelial markers such as E-cadherin, is also required for separation of the optic vesicle from the head ectoderm, and the E-cadherin gene defect leads to the development of a cataract [56]. This gene controls about 190 lower-level genes.

An important stage in lens development is the division of its entire cell population into anterior ectodermal cells and future lens fiber cells. It is believed that this division occurs at the stage of the lens placode. The anterior cells of the optic vesicle form a monolayer of lens epithelial cells located on top of the lens fibers. Between these two layers, there are cells of the equatorial region of the lens, which continuously proliferate and differentiate into secondary lens fibers. The equatorial zone performs a supporting and organizing function for the forming lens fibers, which will be discussed separately. On all sides, the lens is covered by a basement membrane called the lens capsule.

The anterior lens epithelial cells predominantly support the expression of *Hes1*, *Pax6*, *Six3*, *Mab21l1*, *FoxE3*, *Pitx3*, and *MafB* [65]. Wnt/β-catenin signaling participates in this process [51]. Wnts genes signal through Frizzled (Fz) receptors. Wnt/β-catenin signaling and differentiation of the epithelial cells of the anterior portion of the optic vesicle requires the presence of the coreceptor LRP (protein related to the low-density lipoprotein receptor). Moreover, the expression of regulatory genes *SFRPS* (secreted *frizzled* related proteins) and *Dkks* (*Dickkopfs*) is also important for *Wnt-Fz* signaling and lens development [57].

The undifferentiated or pluripotent state of the lens equator cells is maintained by *Hes1*, which regulates the expression of the cell cycle inhibitor p27^{xic1} (cyclin-dependent kinase inhibitor) [26]. This region of lens fiber precursors is also characterized by the expression of *Prox1*. It was shown that the prolifera-

tion and maintenance of specified but not differentiated equatorial cells of lens progenitors involves *FoxE3* [58] and *Sip1*, which belong to the transcription factor family ZFHX1 (zinc finger homeobox proteins), and BMP, *Bmpr1a*, and *Acvr1* (activin A receptor) receptor genes, which are higher than *FoxE3* [59].

Fgf1 and *Fgf2* contribute to the process of differentiation, which is accompanied by a transition of epithelial cells of the lens into lens fibers. Their action is associated with the activation of lens differentiation genes such as *Mab21l1* [55], *FoxE3* [60], *Pitx3* [61, 62], *L-Maf* [54], *MafB* [54], *c-Maf* [63], *Sox1* [34], and *Prox1* [64]. At the same time, preplacodal genes such as *Dlx5*, *Six1*, *Six4*, *Eya1*, and *Eya2*, as well as *Otx2*, are disabled [65]. Then comes the second phase of action of Pax6, which, as was found, activates the α*A*-crystallin gene promoter in mice but represses the β*B1*-crystallin gene in chickens. Pax6 also acts as an activator and repressor of the δ-crystallin gene enhancer in chick embryos [39]. In addition to genes *Six3*, *Prox1*, and *Sox2* and crystallin genes, *Pax6* regulates a diverse range of genes, including genes of specific adhesion molecules (for example, α5β1 integrins, R-cadherin, L1CAM (cell adhesion molecule L1) and JAM1 (junctional adhesion molecule 1), as well as genes for such as proteins paralemmin, molybdopterin, synthase sulfurylase, and neogenin and genes of transcription factors Brg1 (*brahma*-related gene 1), Pitx3, and Etv6 (E26 transformation specific variant 6) [23].

LENS CELL DIFFERENTIATION

In the final developmental stages, the anterior lens epithelial cells form (1) a region of randomly packed cells of a cubic shape; (2) a zone of well-organized cross-sectionally hexagonal cells of future lens fibers; and (3) the so-called germinal zone of progenitor cells arranged in a certain way. The hexagonal shape and the geometry of the honeycomb arrangement of the lens fiber cells allow for their dense stitching, which eliminates the intercellular space, thus minimizing light dispersion and contributing to the high index of refraction. Provided the appropriate migration and appropriate arrangement of elongated fiber cells, this cell packaging requires structural organization of their contractile and adhesive elements, N-cadherin, actin, and myosin. Complexes of N-cadherin and actin via contractile proteins myosin and caldesmon form a hexagonal lattice for basal ends of the fiber cells. Complexes on the basement membrane of the fiber cells were ealso revedal to have paxillin, myosin light chain kinase (MLCK), and focal adhesion kinase (FAK). The maintenance of the hexagonal shape of the lens fiber cells involves protein tropomodulin 1 [66].

In addition to maintaining the hexagonal shape of the lens fiber cells, their arranged extension is also important. A fulcrum is formed in the aforementioned germinal zone in the apical ends of the equatorial epithelial cells. The apices of the hexagonal epithelial cells attach to this fulcrum prior to the differentiation and elongation of the lens fiber cells at the lens equator. At the same time, clusters of phosphorylated proteins Src (sarcoma proto-oncogene tyrosine-kinase), actin, E-cadherin, and receptor tyrosine kinase EphA2 (ephrin type A receptor 2)/ephrin [66] are formed on the apices of the hexagonal fiber cells arranged in meridional rows. Eph/ephrin signaling during embryogenesis is typically responsible for pointing the growth tips of axons and the formation of boundaries between the tissues. The loss of *EphA2* leads to a lack of the lens platform fulcrum, disorganization of the meridional rows, changes in the shape of the equatorial epithelial cells, and ultimately to disturbances in the lens fiber arrangement. EphA2 is an important factor for the activation and phosphorylation of Src and cortactin, which, in turn, capture F-actin at apices of the equatorial hexagonal cells. Thus, the Eph/Src signaling cascade controls morphogenesis from the lens equatorial cells [66]. It is known that *EphA2* or *EphA5* mutations in humans and mice cause cataracts with variable expression or incomplete penetrance. *Ephs* and *ephrins* facilitate cell sorting into opposite compartments, stimulating the completion of cellular communications by establishing gap junctions between cells. Most likely, the EphA2-dependent activation of Src and cortactin is the key signaling that provides the required distribution of F-actin and E-cadherin, leading to changes in the intercellular structure and the basal-lateral shape of cells to that hexagonal when transiting from epithelial to fiber cells at the lens equator.

The lens fiber cells are characterized by the expression of crystallins. The family of crystallins—structural proteins that provide transparency and a high refractive index of the lens is represented in mice by crystallins αA, αB, γA-F, γS, βA1-4, and βB1-3. The cluster γA-F is not expressed in chicken lens crystallins, probably because it is not present in the chicken genome. In addition to γS-crystallins, chicken lenses contain two taxon-specific crystallins: δ1 and δ2. α-Crystallins are normally expressed in both the lens epithelium and the lens fiber cells, and they first appear at the stage of the optic vesicle. The expression of β-crystallin in mice begins at stage E11 and serves an early marker of lens fiber differentiation, while the activation of γ-crystallin genes begins at stage E12.5. The cells of the posterior wall of the optic vesicle elongate quickly, differentiating into primary lens fibers. Cell division stops, followed by cell enucleation. This is accompanied by strong activation of β- and γ-crystallins and all of the genes associated with the differentiation process, such as *Sox1*, *Sox2*, *Sox3* [34], *L-Maf* [54], and *c-Maf* [67], *MIP26* (macrophage infectivity potentiator) and *filensin*. Proteins specific to the lens, CP49 (also known as phakinin) and filensin (or

CP115), are expressed with a starting differentiation of the lens fiber cells and produce distinctive beaded filaments in them.

Crystallin gene regulators with a limited spatial expression pattern consist in factors controlled by genes *Pax6, c-Maf, MafA/L-Maf, MafB, NRL* (gene specific for neural retina-specific leucine zipper gene), *Sox2, Sox1, Prox1, Six3*, factors γFBP-B (γF1-binding protein isoform B) and HSF2 (heat shock transcription factor 2), as well as retinoic acid receptors RARβ/retinoid X receptors (RXRβ) and retinoid-related orphan receptor alpha RORα [23]. All of these factors are differentially expressed in cells of the primary and secondary lens fibers. Thus, regulation of αB-crystallin via heterodimers RARβ/RXRβ is carried out between stages E9.5 and E12.5; the signaling of retinoic acid and retinoids in the lens then disappears. The direct or indirect interaction between Pax6 and nuclear retinoic acid receptors RARβ and RXRβ has been confirmed. These specific DNA-binding transcription activators gather in ensembles on crystallin promoters and more distal regulatory regions of genes containing the appropriate binding sites and carry out their specific functions. For example, they neutralize the inhibitory effect of chromatin and collect necessary common transcription factors, including RNA polymerase II and coactivator CBP/p300, which consist of protein p300 and CREB-binding protein, which havs histone acetylase activity and leads to stimulation of CAMP-dependent protein kinase, and Brg1, the catalytic subunit of the SWI/SNF (SWItch/Sucrose NonFermentable) complex, which is specific to histone H3 lysine 4 methyltransferase. All this leads to full activation of the crystallin gene transcription apparatus.

As a result, lens fiber cells lose all membrane-bound organelles. These cells quit the cell cycle, mainly due to the expression of inhibitors of cyclin-dependent kinases Cdkn1b/p27 and Cdkn1c/p57. Other cell cycle regulators, three D-type cyclins, continue to be expressed during the lens differentiation, while cyclin D2 is the most highly expressed cyclin in the posterior optic vesicle [68]. Its expression in the postmitotic lens fiber cells is suppressed, which is needed to maintain their postmitotic state [69]. *GATA-3*, acting on cyclin-dependent kinase inhibitors Cdkn1b/p27 and Cdkn1c/p57, which end the cell cycle, plays an important role in lens fiber cell differentiation [70]. The expression of GATA-3 in normally developing lens fiber cells is negatively directly or indirectly controlled via *c-Maf*. To quit the mitotic cycle, the cells also require a common key cell cycle regulator retinoblastoma protein, pRb. The interaction between *pRb* and *Pax6* has been demonstrated.

In the developing optic vesicle, *L-Maf* is predominantly expressed in the lens fibers, while the preferred location of *c-Maf* expression lies in the anterior lens epithelium. The expression of *MafB* occurs after the formation of the optic vesicle in the lens epithelium and fibers [71, 72]. The ectopic expression of all of the tested lens-specific genes is induced under the ectopic expression of *L-Maf* in the head ectoderm of chick embryos and the cultivation of neural retina cells. This includes all of the crystallin classes, *c-Maf*, *MafB*, *Prox1*, cyclin-dependent kinase inhibitor p27kip1, and the lens fiber-specific water channel protein encoded by *MIP* [72].

In mice, *c-Maf* is required for lens differentiation, while the functions of *L-Maf* and *MafB* can be compensated by *c-Maf* [73]. In mice with knockout for *c-Maf*, the lens fibers are not formed, the lens fiber-specific expression of γ-crystallins (γ*A*, γ*B*, γ*C*, γ*D*, γ*E*, and γ*F*) is completely absent, and the expression of other classes of crystallins (α and β) is greatly reduced, while *Prox1* gene expression is not changed.

Prox1 controls the cell cycle and cell elongation during lens fiber differentiation. Changes in Prox1 protein lead to disturbances of its intracellular localization during lens development [64]. In mice, *Prox1* expression requires the expression of *Pax6* and *Six3* in the lens placode and later FGFR (*Fgfr1-3*) receptor signaling in the optic vesicle [74]. It was found that mice with knockout for *Prox1* [75] have no lens fiber-specific expression of genes *p27kip1* and *p57kip2* and no expression of some γ-crystallins (γ*B* and γ*D*), and E-cadherin gene expression, which is characteristic of the anterior lens epithelium, spreads to posterior cells. However, the expression of other crystallins remains normal.

An important role in the differentiation process belongs to the functioning of proteins containing in their structure the PDZ domain (an acronym of the first letters of proteins PSD95, Dlg1, and Zo-1). Due to their multiple domains for protein–protein interactions, the PDZ family proteins are believed to serve as scaffold molecules capable of collecting large macromolecular signaling complexes at the cell membrane. Proteins Dlg-1 (large discs), Scrib (protein polarity Scribble), and numerous other PDZ proteins are expressed throughout the eye lens. Proteins Dlg-1 and Scrib are localized together with one another and with cell adhesion proteins E-cadherin and N-cadherin and apical protein ZO-1 (zonula occludens, tight junction protein 1) [76]. Defects arising from the loss of the Dlg-1 function are associated with disturbances in cell adhesion, cytoskeletal organization, and apical-basal polarity factors. Loss of the *Dlg-1* gene function also reduces levels of factors α-catenin, MIP26, and pERK1/2 (extracellular signal-regulated kinase 1/2), which are essential for the maintenance of the normal cellular architecture and differentiation of lens fiber cells [77]. In addition, the actin cytoskeleton organi-

zation gets violated, especially in the apical regions of the lens fiber cells, in the region of attachment to the capsule, wherein protein Dlg-1 is usually found in high concentrations and is localized in conjunction with N-cadherin, Src, and cortactin [76]. The similarity of *Dlg-1*-deficient and *Cdh2*-deficient lenses supports the hypothesis that Dlg-1 is a modulator of N-cadherin function.

In mammalian embryos, E-cadherin and N-cadherin genes are expressed generally in the epithelial cells of undifferentiated lenses. The differentiated cells of the lens fibers express only N-cadherin [78]. N-Cadherin compounds of the epithelial cells of undifferentiated lenses are arranged in the form of a nascent immature type of compounds [78] located on the apices of the plate-shaped protrusions between the lateral cell membranes of the epithelial lens cells. Maturation of these N-cadherin compounds is related in time to the initiation of the lens differentiation. It is assumed that kinase for c-Src (C-terminal sarcoma tyrosine) CSK (C-terminal Src kinase) regulates the initiation of the lens cell differentiation by preventing the maturation of N-cadherin compounds. The cadherin complex contains many targets for tyrosine kinase c-Src. These include cadherin receptors, β-catenin, γ-catenin, and p120-catenin. Suppression of the kinase c-Src (CSK) activity also induces the expression of cyclin-dependent kinase inhibitors p27 and p57, cell cycle arrest, and lens differentiation initiation [79]. The regulation of the activity of protein-tyrosine kinase Fyn of the Src family is central for the cells to decide "to stop proliferation and move towards differentiation" [80].

Mature N-cadherin compounds resulting from the activity of protein-tyrosine kinase Fyn serve as places for the assembly of cortical actin filaments essential for both the organization and elongation of the lens fiber cells. Cortical actin is important for generating moving forces and determining the cell shape [78]. Signaling via lower-level signaling effector kinase Fyn, phosphoinositide 3-kinase PI3K, and its lower-level effector Rac (Ras-related protein of the Rho family of GTPases, small signaling G proteins) provides the organization of cortical actin structures and controls the elongation of differentiating lens fiber cells [80]. During the maturation of lens fiber cells, nonmuscle myosin assembly defects normally give rise to juvenile cataracts, pointing to the importance of myosin for the elongation of the lens fiber cells [81].

In mature lens fibers, protein periaxin (Prx), which has the PDZ domain, comprises adherens junctions, together with other proteins involved in the organization of membranes, such as ankyrin-B, spectrin, NrCAM (nerve cell adhesion molecule), filensin, ezrin, and desmoyokin. Under knockout for *Prx*, mouse lenses exhibit disturbances in the hexagonal packing of lens fiber cells, skeleton, and membrane stability [82]. The organization of the cytoskeleton may also be violated under the suppression of the Rho GTPase activity in the lens fiber cells [83]. Connexins Cx46 and Cx50 expressed in human lens fiber cells in the lens core tightly connect them, which is essential for the growth and transparency of the lens [84].

LENS AND miRNA

Some miRNA molecules are expressed in many tissues, while others are expressed strongly in certain tissues; miRNA is found at high levels in the cornea and lens of mice [85, 86].

During the cornea and lens development, the abundant expression of *Dicer* (RNase III endonuclease) is important for the production and preservation of function of mature miRNA molecules in the lens [87]. The absence of this gene in mouse embryos with the conditional null mutation *DicerCN* (*Dicer conditional null*) causes progressive degeneration of the lens, followed by microphthalmia. Analysis of the differential gene expression in the lens of mice *Dicer CN* at stage E13.5 showed that they expressed many genes involved in the implementation of the so-called P53 pathway, including genes for Tp53inp1 (tumor protein p53 inducible nuclear protein 1), Cdkn1a (p21Cip), serpin2, and Tnfrsf10A (tumor necrosis factor receptor superfamily, member 10a), which are key regulators of cell death and cell cycle arrest [88], as well as genes for the higher-level regulators and/or modifiers P53 [89]. It is assumed that lens development regulation through miRNA consists of forming lower-level sequential activation of lens-specific transcription factors. A decrease in the expression of β- and γ-crystallin genes contribute to degeneration of the lens in *Dicer CN* mice. Thus, a decrease in the expression of lens-specific γS-crystallin, which is usually present at a high level in the lens fiber cells, causes degeneration of the lens cells, resulting in cataracts [90]. *Fgfr2* gene expression is also suppressed in the lens of the *Dicer CN* mutants [91]. Perhaps the regulation of the Fgfr2 factor level in developing lenses may be the pathway through which gene *Dicer* and miRNA are involved in the lens development. *Itgb8* (integrin beta-8) is an example of gene activation in the lens of the *Dicer CN* mutants, which is unusual for normal development. Other genes activated in the lens of *Dicer CN* are involved in the development of various other tissues. So, lens miRNAs may act by limiting the expression of genes that determine the proper lens development. The identification of target genes for miRNAs will identify specific the roles of many miRNAs that are dynamically expressed in the developing lens and cornea.

CONCLUSIONS

We have examined the genes involved in the development of a lens, the anlage of which is only a part of the region of the ocular ectoderm of the head. It is known that mutations in the considered genes, according to their stage- and tissue-specificity, cause developmental disorders of the lens, from its complete absence to opacification (in different types of cataracts). Thus, there is a certain hierarchy of lens anomalies that apparently corresponds to the hierarchical position of the genes involved in its development (genes of embryonic induction, specification, and differentiation and functional genes). The top of this hierarchical chain is likely to be occupied by the genes responsible for compartmentalization of the ocular ectoderm, which is apparently carried out on the basis of the existing positional information. This information is usually provided by means of morphogen gradients, for example, retinoic acid, the gene activity, as well as receptor activity, of which is observed in the lens anlage. The gradients of different morphogens apparently maintain further differential activity of certain genes in certain regions. This is accompanied by certain splitting or regionalization of the tissue and isolation of the lens placode divided, in turn, into the anterior and posterior compartments of the optic vesicle and the lens. The cells of these optic vesicle compartments at some stage stop their proliferation (except for the lens equator) and begin to differentiate as a result of the activation of many different groups of genes involved in morphogenesis of cells, their connection and packaging, and their viability and functions. Unfortunately, almost nothing is known about how and through what morphogens the positional information for the regionalization of the lens is provided.

Further research in identifying the interactions between signaling systems, transcription factors, and noncoding RNAs participating in the formation of the lens is required to create a more complete picture of lens development.

REFERENCES

1. Mglinets, V.A., Molecular genetics of development of cornea, *Russ. J. Genet.,* 2015, vol. 51, no. 1, pp. 1–8.
2. Mglinets, V.A., Formation of preplacodal area and placodes for some sensorial structures in animals, *Med. Genet.*, 2009, vol. 8, no. 5, pp. 3–10.
3. Avbar, M.J. and Mayor, R., Early induction of neural crest cells: lessons learned from frog, fish and chick, *Curr. Opin. Genet. Dev.*, 2002, vol. 12, pp. 452–458.
4. Grocott, T., Johnson, S., Bailey, A.P., and Streit, A., Neural crest cells organize the eye via TGF-β and canonical Wnt signalling, *Nat. Commun.*, 2011, vol. 2, no. 265, pp. 1–6.
5. Feledy, J.A., Beanan, M.J., Sandoval, J.J., et al., Inhibitory patterning of the anterior neural plate in *Xenopus* by homeodomain factors Dlx3 and Msx1, *Dev. Biol.*, 1999, vol. 212, no. 2, pp. 455–464.
6. Woda, J.M., Pastagia, J., Mercola, M., and Artinger, K.B., Dlx proteins position the neural plate border and determine adjacent cell fates, *Develop.*, 2003, vol. 130, no. 2, pp. 331–342.
7. Bhattacharyya, S., Bailey, A.P., Bronner-Fraser, M., and Streit, A., Segregation of lens and olfactory precursors from a common territory: cell sorting and reciprocity of *Dlx5* and *Pax6* expression, *Dev. Biol.*, 2004, vol. 271, no. 2, pp. 403–414.
8. Quint, E., Zerucha, T., and Ekker, M., Differential expression of orthologous *Dlx* genes in zebrafish and mice: implications for the evolution of the *Dlx* homeobox gene family, *J. Exp. Zool.*, 2000, vol. 288, no. 3, pp. 235–241.
9. Litsiou, A., Hanson, S., and Streit, A., A balance of FGF, Wnt, and BMP signalling positions the future placode territory in the head, *Develop.*, 2005, vol. 132, pp. 4051–4062.
10. Bessarab, D.A., Chong, S.W., and Korzh, V., Expression of zebrafish six1 during sensory organ development and myogenesis, *Dev. Dyn.*, 2004, vol. 230, no. 4, pp. 781–786.
11. Sato, S., Ikeda, K., Shioi, G., et al., Conserved expression of mouse *Six1* in the pre-placodal region (PPR) and identification of an enhancer for the rostral PPR, *Dev. Biol.*, 2010, vol. 344, no. 1, pp. 158–171.
12. Ghanbari, H., Seo, H.C., Fjose, A., and Brandli, A.W., Molecular cloning and embryonic expression of *Xenopus Six* homeobox genes, *Mech. Dev.*, 2001, vol. 101, nos. 1–2, pp. 271–277.
13. McLarren, K.W., Litsiou A., and Streit, A., DLX5 positions the neural crest and preplacode region at the border of the neural plate, *Dev. Biol.*, 2003, vol. 259, no. 1, pp. 34–47.
14. David, R., Ahrens, K., Wedlich, D., and Schlosser, G., *Xenopus Eya1* demarcates all neurogenic placodes as well as migrating hypaxial muscle precursors, *Mech. Dev.*, 2001, vol. 103, nos. 1–2, pp. 189–192.
15. Ishihara, T., Ikeda, K., Sato, S., et al., Differential expression of *Eya1* and *Eya2* during chick early embryonic development, *Gene Expr. Patterns*, 2008, vol. 8, no. 5, pp. 357–367.
16. Ishihara T., Sato S., Ikeda, K., et al., Multiple evolutionarily conserved enhancers control expression of Eya1, *Dev. Dyn.*, 2008, vol. 237, pp. 3142–3156.
17. Ahrens, K. and Schlosser, G., Tissues and signals involved in the induction of placodal *Six1* expression in *Xenopus laevis*, *Dev. Biol.*, 2005, vol. 288, pp. 40–59.
18. Morgan, R., Sohal, J., Paleja, M., and Pettengell, R., Pbx genes are required in *Xenopus* lens development, *Int. J. Dev. Biol.*, 2004, vol. 48, no. 7, pp. 623–627.
19. Zhu, C.C., Dyer, M.A., Uchikawa, M., et al., Six3-mediated auto repression and eye development requires its interaction with members of the Groucho-related family of co-repressors, *Develop.*, 2002, vol. 129, no. 12, pp. 2835–2849.

20. Purcell, P., Oliver, G., Mardon, G., et al., *Pax6*-dependence of *Six3*, *Eya1,* and *Dach1* expression during lens and nasal placode induction, *Gene Expr. Patterns*, 2005, vol. 6, no. 1, pp. 110–118.
21. Goudreau, G., Petrou, P., Reneker, L.W., et al., Mutually regulated expression of *Pax6* and *Six3* and its implications for the *Pax6* haploinsufficient lens phenotype, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, vol. 99, no. 13, pp. 8719–8724.
22. Uchikawa, M., Yoshida, M., Iwafuchi-Doi, M., et al., B1 and B2 *Sox* gene expression during neural plate development in chicken and mouse embryos: universal versus species-dependent features, *Dev. Growth Differ.*, 2011, vol. 53, pp. 761–771.
23. Cvekl, A., Yang, Y., Chauhan, B.K., and Cveklova, K., Regulation of gene expression by Pax6 in ocular cells: a case of tissue-preferred expression of crystallins in lens, *Int. J. Dev. Biol.*, 2004, vol. 48, nos. 8–9, pp. 829–844.
24. Martinez-Morales, J.R., Signore, M., Acampora, D., et al., *Otx* genes are required for tissue specification in the developing eye, *Develop.*, 2001, vol. 128, pp. 2019–2030.
25. Zhou, X., Hollemann, T., Pieler, T., et al., Cloning and expression of *Six3*, the *Xenopus* homologue of murine *Six3*, *Mech. Dev.*, 2000, vol. 91, pp. 327–330.
26. Murato, Y. and Hashimoto, C., *Xhairy2* functions in *Xenopus* lens development by regulating *p27(xic1)* expression, *Dev. Dyn.*, 2009, vol. 238, pp. 2179–2192.
27. Dutta, S., Dietrich, J.E., Aspock, G., et al., Pitx3 defines an equivalence domain for lens and anterior pituitary placode, *Develop.*, 2005, vol. 132, pp. 1579–1590.
28. Liu, W., Lagutin, O.V., Mende, M., et al., Six3 activation of Pax6 expression is essential for mammalian lens induction and specification, *EMBO J.*, 2006, vol. 25, pp. 5383–5395.
29. Schlosser, G., Induction and specification of cranial placodes, *Dev. Biol.*, 2006, vol. 294, pp. 303–305.
30. Kamachi, Y., Uchikawa, M., Tanouchi, A., et al., Pax6 and SOX2 form a co-DNA-binding partner complex that regulates initiation of lens development, *Genes Dev.*, 2001, vol. 15, no. 10, pp. 1272–1286.
31. Donner, A.L., Episkopou, V., and Maas, R.L., Sox2 and pou2fl interact to control lens and olfactory placode development, *Dev. Biol.*, 2007, vol. 303, pp. 784–799.
32. Zygar, C.A., Cook, T.L., and Grainger, R.M., Gene activation during early stages of lens induction in *Xenopus*, *Develop.*, 1998, vol. 125, no. 17, pp. 3509–3519.
33. Christophorou, N.A., Bailey, A.P., Hanson, S., and Streit, A., Activation of *Six1* target genes is required for sensory placode formation, *Dev. Biol.*, 2009, vol. 336, no. 2, pp. 327–336.
34. Kamachi, Y., Uchikawa, M., Collignon, J., et al., Involvement of *Sox1*, *2* and *3* in the early and subsequent molecular events of lens induction, *Develop.*, 1998, vol. 125, no. 13, pp. 2521–2532.
35. Zhang, X., Friedman, A., and Heaney, S., et al., Meis homeoproteins directly regulate *Pax6* during vertebrate lens morphogenesis, *Genes Dev.*, 2002, vol. 16, no. 16, pp. 2097–2107.
36. Aota, S., Nakajima, N., Sakamoto, R., et al., *Pax6* autoregulation mediated by direct interaction of Pax6 protein with the head surface ectoderm-specific enhancer of the mouse *Pax6* gene, *Dev. Biol.*, 2003, vol. 257, no. 1, pp. 1–13.
37. Reza, H.M., Ogino, H., and Yasuda, K., L-Maf, a downstream target of *Pax6*, is essential for chick lens development, *Mech. Dev.*, 2002, vol. 116, nos. 1–2, pp. 61–73.
38. Shimada, N., Aya-Murata, T., Reza, H.M., and Yasuda, K., Cooperative action between L-Maf and Sox2 on δ-*crystallin* gene expression during chick lens development, *Mech. Dev.*, 2003, vol. 120, no. 4, pp. 455–465.
39. Muta, M., Kamachi, Y., Yoshimoto, A., et al., Distinct roles of SOX2, Pax6, and Maf transcription factors in the regulation of lens-specific δ_1-*crystallin* enhancer, *Genes Cells*, 2002, vol. 7, no. 8, pp. 791–805.
40. Ogino, H. and Yasuda, K., Sequential activation of transcription factors in lens induction, *Dev. Growth Differ.*, 2000, vol. 42, pp. 437–448.
41. Plouhinec, J.L., Leconte, L., Sauka-Spengler, T., et al., Comparative analysis of gnathostome *Otx* gene expression patterns in the developing eye: implications for the functional evolution of the multigene family, *Dev. Biol.*, 2005, vol. 278, no. 2, pp. 560–575.
42. Andreazzoli, M., Gestri, G., Cremisi, F., et al., *Xrx1* controls proliferation and neurogenesis in *Xenopus* anterior neural plate, *Develop.*, 2003, vol. 130, no. 21, pp. 5143–5154.
43. Ogino, H., Fisher, M., and Grainger, R.M., Convergence of a head-field selector Otx2 and Notch signaling: a mechanism for lens specification, *Develop.*, 2008, vol. 135, pp. 249–258.
44. Medina-Martinez, O., Shah, R., and Jamrich, M., *Pitx3* controls multiple aspects of lens development, *Dev. Dyn.*, 2009, vol. 238, pp. 2193–2201.
45. Lee, H.Y., Wroblewsk, E., Philips, G.T., et al., Multiple requirements for *Hes1* during early eye formation, *Dev. Biol.*, 2005, vol. 284, no. 2, pp. 464–478.
46. Smith, A.N., Miller, L.A., Radice, G., et al., Stage-dependent modes of *Pax6–Sox2* epistasis regulate lens development and eye morphogenesis, *Develop.*, 2009, vol. 136, no. 17, pp. 2977–2985.
47. Lang, R.A., Pathways regulating lens induction in the mouse, *Int. J. Dev. Biol.*, 2004, vol. 48, nos. 8–9, pp. 783–791.
48. Kleinjan, D.A., Seawright, A., Mella, S., et al., Long-range downstream enhancers are essential for *Pax6* expression, *Dev. Biol.*, 2006, vol. 299, no. 2, pp. 563–581.
49. Rowan, S., Siggers, T., Lachke, S.A., et al., Precise temporal control of the eye regulatory gene *Pax6* via

enhancer-binding site affinity, *Genes Dev.*, 2010, vol. 24, no. 10, pp. 980–985.

50. Faber, S.C., Dimanlig, P., Makarenkova, H.P., et al., *Fgf* receptor signaling plays a role in lens induction, *Develop.*, 2001, vol. 128, no. 22, pp. 4425–4438.
51. Machon, O., Kreslova, J., Ruzickova, J., et al., Lens morphogenesis is dependent on *Pax6*-mediated inhibition of the canonical Wnt/β-catenin signaling in the lens surface ectoderm, *Genesis*, 2010, vol. 48, no. 2, pp. 86–95.
52. Smith, A.N., Miller, L.A., Song, N., et al., The duality of β-catenin function: a requirement in lens morphogenesis and signaling suppression of lens fate in periocular ectoderm, *Dev. Biol.*, 2005, vol. 285, no. 2, pp. 477–489.
53. Klimova, L. and Kozmik, Z., Stage-dependent requirement of neuroretinal Pax6 for lens and retina development, *Develop.*, 2014, vol. 141, pp. 1292–1302.
54. Ishibashi, S. and Yasuda, K., Distinct roles of maf genes during *Xenopus* lens development, *Mech. Dev.*, 2001, vol. 101, pp. 155–166.
55. Yamada, R., Mizutani-Koseki, Y., Hasegawa, T., et al., Cell-autonomous involvement of *Mab21l1* is essential for lens placode development, *Develop.*, 2003, vol. 130, no. 9, pp. 1759–1770.
56. Manthey, A.L., Lachke, S.A., FitzGerald, P.G., et al., Loss of Sip1 leads to migration defects and retention of ectodermal markers during lens development, *Mech. Dev.*, 2014, vol. 131, pp. 86–110.
57. Chen, Y., Stump, R.J.W., Lovicu, F., and McAvoy, J.W., Expression of Frizzled and secreted frizzled-related proteins (Sfrps) during mammalian lens development, *Int. J. Dev. Biol.*, 2004, vol. 48, nos. 8–9, pp. 867–877.
58. Kenyon, K.L., Moody, S.A., and Jamrich, M., A novel fork head gene mediates early steps during *Xenopus* lens formation, *Develop.*, 1999, vol. 126, no. 22, pp. 5107–5116.
59. Rajagopal, R., Huang, J., Dattilo, L.K., et al., The type I BMP receptors, *Bmpr1a* and *Acvr1*, activate multiple signaling pathways to regulate lens formation, *Dev. Biol.*, 2009, vol. 335, no. 2, pp. 305–316.
60. Shi, X., Luo, Y., Howley, S., et al., Zebrafish *foxe3*: roles in ocular lens morphogenesis through interaction with *pitx3*, *Mech. Dev.*, 2006, vol. 123, no. 10, pp. 761–782.
61. Semina, E.V., Murray, J.C., Reiter, R., et al., Deletion in the promoter region and altered expression of *Pitx3* homeobox gene in aphakia mice, *Hum. Mol. Genet.*, 2000, vol. 9, no. 11, pp. 1575–1585.
62. Zilinski, C.A., Shah, R., Lane, M.E., and Jamrich, M., Modulation of zebrafish *pitx3* expression in the primordia of the pituitary, lens, olfactory epithelium and cranial ganglia by hedgehog and nodal signaling, *Genesis*, 2005, vol. 41, no. 1, pp. 33–40.
63. Reza, H.M. and Yasuda, K., Lens differentiation and *crystallin* regulation: a chick model, *Int. J. Dev. Biol.*, 2004, vol. 48, pp. 805–817.
64. Duncan, M.K., Cui, W., Oh, D.J., and Tomarev, S.I., Prox1 is differentially localized during lens development, *Mech. Dev.*, 2002, vol. 112, nos. 1–2, pp. 195–198.
65. Ogino, H., Ochi, H., Reza, H.M., and Yasuda, K., Transcription factors involved in lens development from the preplacodal ectoderm, *Dev. Biol.*, 2012, vol. 363, no. 2, pp. 333–347.
66. Cheng, C., Ansari, M.M., Cooper, J.A., and Gong, X., EphA2 and Src regulate equatorial cell morphogenesis during lens development, *Develop.*, 2013, vol. 140, pp. 4237–4245.
67. Kajihara, M., Kawauchi, S., Kobayashi, M., et al., Isolation, characterization, and expression analysis of zebrafish large Mafs, *J. Biochem.*, 2001, vol. 129, no. 1, pp. 139–146.
68. Zhang, P., Wong, C., DePinho, R.A., et al., Cooperation between the Cdk inhibitors p27(KIP1) and p57(KIP2) in the control of tissue growth and development, *Genes Dev.*, 1998, vol. 12, pp. 3162–3167.
69. Gomez, L.E., Liegeois, N.J., Zhang, P., et al., Cyclin D- and E-dependent kinases and the p57(KIP2) inhibitor: cooperative interactions in vivo, *Mol. Cell Biol.*, 1999, vol. 19, pp. 353–363.
70. Maeda, A., Nakano, T., Moriguchi, T., et al., Transcription factor GATA-3 is essential for lens development, *Dev. Dyn.*, 2009, vol. 238, pp. 2280–2291.
71. Reza, H.M. and Yasuda, K., Roles of Maf family proteins in lens development, *Dev. Dyn.*, 2004, vol. 229, pp. 440–448.
72. Reza, H.M., Urano, A., Shimada, N., and Yasuda, K., Sequential and combinatorial roles of maf family genes define proper lens development, *Mol. Vis.*, 2007, vol. 13, pp. 18–30.
73. Takeuchi, T., Kudo, T., Ogata, K., et al., Neither *MafA/L-Maf* nor *MafB* is essential for lens development in mice, *Genes Cells*, 2009, vol. 14, no. 8, pp. 941–947.
74. Zhao, H., Yang, T., Madakashira, B.P., et al., Fibroblast growth factor receptor signaling is essential for lens fiber cell differentiation, *Dev. Biol.*, 2008, vol. 318, no. 2, pp. 276–288.
75. Wigle, J.T., Chowdhury, K., Gruss, P., and Oliver, G., *Prox1* function is crucial for mouse lens-fibre elongation, *Nat. Genet.*, 1999, vol. 21, no. 3, pp. 318–322.
76. Nguyen, M.M., Rivera, C., and Griep, A.E., Localization of PDZ domain containing proteins Discs Large-1 and Scribble in the mouse eye, *Mol. Vis.*, 2005, vol. 11, pp. 1183–1199.
77. Rivera, C., Griep, A.E., Yamben, I.F., et al., Cell-autonomous requirements for Dlg-1 for lens epithelial cell structure and fiber cell morphogenesis, *Dev. Dyn.*, 2009, vol. 238, pp. 2292–2308.
78. Leonard, M., Zhang, L., Zhai, N., et al., Modulation of N-cadherin junctions and their role as epicenters of differentiation-specific actin regulation in the developing lens, *Dev. Biol.*, 2011, vol. 349, pp. 363–377.

79. Walker, J.L., Zhang, L., and Menko, A.S., Transition between proliferation and differentiation for lens epithelial cells is regulated by Src family kinases, *Dev. Dyn.*, 2002, vol. 224, pp. 361–372.

80. Leonard, M., Zhang, L., Bleaken, B.M., and Menko, A.S., Distinct roles for N-cadherin linked c-Src and fyn kinases in lens development, *Dev. Dyn.*, 2013, vol. 242, no. 5, pp. 469–484.

81. Hansen, L., Comyn, S., Mang, Y., et al., The myosin chaperone UNC45B is involved in lens development and autosomal dominant juvenile cataract, *Eur. J. Hum. Genet.*, 2014, vol. 22, no. 11, pp. 1290–1297.

82. Maddala, R., Skiba, N.P., Lalane, R., et al., Periaxin is required for hexagonal geometry and membrane organization of mature lens fibers, *Dev. Biol.*, 2011, vol. 357, no. 1, pp. 179–190.

83. Maddala, R., Reneker, L.W., Pendurthi, B., and Rao, P.V., Rho GDP dissociation inhibitor-mediated disruption of Rho GTPase activity impairs lens fiber cell migration, elongation and survival, *Dev. Biol.*, 2008, vol. 315, no. 2, pp. 217–231.

84. Gong, X., Cheng, C., and Xia, C.H., Connexins in lens development and cataractogenesis, *J. Membr. Biol.*, 2007, vol. 218, nos. 1–3, pp. 9–12.

85. Ryan, D.G., Oliveira-Fernandes, M., and Lavker, R.M., MicroRNAs of the mammalian eye display distinct and overlapping tissue specificity, *Mol. Vis.*, 2006, vol. 12, pp. 1175–1184.

86. Karali, M., Peluso, I., Marigo, V., and Banfi, S., Identification and characterization of microRNAs expressed in the mouse eye, *Invest. Ophthalmol. Vis. Sci.*, 2007, vol. 48, pp. 509–515.

87. Li, Y. and Piatigorsky, J., Targeted deletion of dicer disrupts lens morphogenesis, corneal epithelium stratification, and whole eye development, *Dev. Dyn.*, 2009, vol. 238, pp. 2388–2400.

88. He, L., He, X., Lim, L.P., et al., A microRNA component of the p53 tumor suppressor network, *Nature*, 2007, vol. 447, pp. 1130–1134.

89. Rane, S., He, M., Sayed, D., et al., Downregulation of Mir-199a derepresses hypoxia-inducible factor-1{alpha} and Sirtuin 1 and recapitulates hypoxia preconditioning in cardiac myocytes, *Circ. Res.*, 2009, vol. 104, pp. 879–886.

90. Sun, H., Ma, Z., Li, Y., et al., Gamma-S crystallin gene (CRYGS) mutation causes dominant progressive cortical cataract in humans, *J. Med. Genet.*, 2005, vol. 42, pp. 706–710.

91. Robinson, M.L., An essential role for FGF receptor signaling in lens development, *Semin. Cell Dev. Biol.*, 2006, vol. 17, pp. 726–740.

Translated by K. Lazarev